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CHRONIC STRESS IMPAIRMENT OF PREFRONTAL CORTEX ENERGY METABOLISM IS RELATED TO GENDER AND CAN NOT BE AMELIORATED BY ANTIDEPRESANT FLUOXETINE

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Abstract

The activity of cytochrome c oxidase correlates with neuronal functional activity and is considered as an ideal marker for examining the effects of antidepressant treatment on brain metabolism. We investigated gender specific effects of antidepressant fluoxetine on cytochrome c oxidase activity in the mitochondria of prefrontal cortex (PFC) of chronically isolated female and male Wistar rats. Our results showed that chronic psychosocial isolation (CPSI) increased cytochrome c oxidase activity in female PFC, while in males, this activity was decreased. Fluoxetine treatment did not normalize cytochrome c oxidase activity in either CPSI females or CPSI males. Our data suggest that the pattern of PFC energy metabolism impairment by CPSI is related to gender, but that fluoxetine treatment was unable to ameliorate these defects.

Introduction

Beside well established monoamine theory of depression, an alternative theory has been proposed, called ‘‘the mitochondrial dysfunction hypothesis’’, suggesting that impaired functions of mitochondria are associated with psychiatric conditions such as bipolar disorder [1], major depression and a spectrum of affective disorders [2].

The complex IV or cytochrome c oxidase (cyt c oxidase) is the terminal respiratory enzyme in the mitochondrial electron transport chain whose activity correlates with ATP synthesis and serves as an endogenous metabolic marker for neuronal functional activity [3]. Moreover, its activity is considered as an ideal marker for examining the effects of antidepressant treatment on brain metabolism [4].

Since a novel therapeutic strategy is to evaluate the effects of antidepressants in regard to their capability to alter/correct energy parameters, in this study we examined the sex dependent effect of antidepressant fluoxetine on cyt c oxidase activity in the mitochondria of prefrontal cortex of chronically isolated female and male Wistar rats.

Experimental

Animals and treatment

The experiments were performed on adult (3 months old) Wistar female and male rats. The animals were divided into four experimental groups: two control groups

(n=12, each) and two stressed groups (n=12, each), respectively. The control groups were intraperitoneally treated with the mass-adjusted volume of vehicle (VEH; water) - *control/vehicle group* or with fluoxetine (5mg/kg per day) - *control/fluoxetine group* between 9:00 a.m. and 9:30 a.m. for 21 days. In the stressed groups, animals were subjected to the chronic psychosocial isolation (CPSI) for 21 days and were intraperitoneally injected with the mass-adjusted volume of vehicle (VEH; water) - *CPSI/vehicle group* or with fluoxetine (5mg/kg per day) - *CPSI/fluoxetine group* between 9:00 a.m. and 9:30 a.m. for another 21 days.

Measurement of cytochrome c *oxidase activity*

The activity of cyt c oxidase was assayed in the animal's prefrontal cortex according to Rustin et al. [5] and measured by following the decrease in absorbance due to the oxidation of previously reduced cytochrome c at 550 nm. The activities of cyt c oxidase were calculated as nmol/min/mg protein.

Statistical analysis

Data are presented as a mean ± SEM and in each gender were analyzed with two-way analyses of variance (ANOVA). To determine statistically significant gender differences we used three-way analyses of variance (ANOVA) employing stress, fluoxetine and sex as the factors. All statistically significant differences are given as $p < 0.05$, including $p < 0.01$ and 0.001.

Results and Discussion

Cytochrome c oxidase activity

It has been described that chronic stress inhibits the cyt c oxidase activity and impairs energy metabolism in rat prefrontal cortex and hippocampus [6]. In our experiments, the CPSI significantly increased the cyt c oxidase activity in the female mitochondria ($F=48.10$, $p<0.05$) (Figure 1), while in the males, the CPSI significantly decreased the cyt c oxidase activity ($F=19.33$, $p<0.05$). Our results indicated gender specific response to CPSI regarding cyt c oxidase activity.

A number of studies reported that antidepressants cause impairment in mitochondrial function [7, 8]. In our study, the FLU treatment of the control females significantly increased the activity of cyt c oxidase ($F=16.46$, $p<0.05$), while, in the control males, it significantly decreased it ($F=18.46$, $p<0.05$). The subsequent FLU treatment of either CPSI females or males did not alter cyt c oxidase activity.

Moreover, the statistical analyses showed the significant gender difference regarding the activity of cyt c oxidase ($F=43.65$, $p<0.05$). Namely, the activity of cyt c oxidase in the male control group was significantly increased in comparison to the female respective control ($p<0.05$), while in response to CPSI, it was significantly decreased in males (sex x stress interaction, $F=54.87$, $p<0.05$). Furthermore, FLU treatment of either control (sex x FLU interaction, $F=33.01$, $p<0.05$) or either CPSI (sex x stress x FLU interactions, $F=20.24$, $p<0.05$) animals showed significant gender difference regarding cyt c oxidase activity.

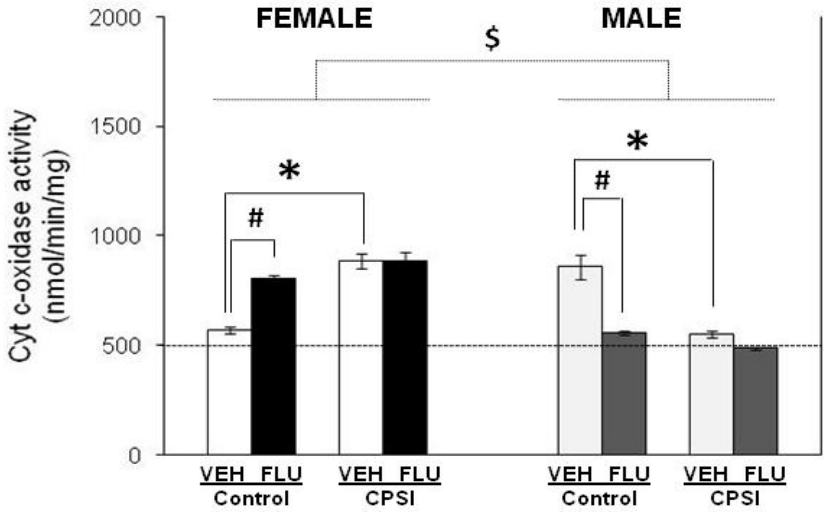

Figure 1. Cytochrom c oxidase activity (nmol/min/mg) in the prefrontal cortex of female and male Wistar rats treated for 21 days with vehicle (VEH) or fluoxetine (FLU) in basal condition (control) or exposed to the chronic psychosocial isolation (CPSI) for 21 days and treated with vehicle or fluoxetine for 21 days. Data are presented as mean ± SEM. (* *vs.* CPSI, # *vs.* fluoxetine treatment, $ female *vs*. male).

Conclusion

Impairment of energy metabolism under chronic psychosocial isolation is related to gender and could not be ameliorated by fluoxetine administration. However, it remains to be seen if the effects of fluoxetine on the mitochondrial respiratory chain are specific to changes in animal behavior or the side effects of antidepressant e.g. apoptosis.

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